

Pediatric Ocular Motility Disorders

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Abstract

Ophthalmoplegia in children, be it congenital or acquired has many potential causes. Various clinical and ophthalmological features supported by targeted investigations aid in solving the diagnostic dilemma in most clinically challenging situations. The clinical presentation of ocular motility disorders can be variable in children and approach to clinical examination can be difficult because children do not necessarily cooperate all the time. A comprehensive multidisciplinary involvement of the strabismologist, neurologist, paediatric physicians and neurosurgeons may be required. Treatment strategy needs to be carefully decided considering the risk-benefit ratio amongst the available therapeutic medical and surgical options. Response to treatment can be unpredictable and a close evaluation with frequent follow-ups is mandatory. This review highlights the etio-pathogenesis, clinical presentation, investigational and management approach to children with these ocular motility disorders.

Keywords: *Pediatric Ophthalmoplegia; Childhood Ocular Motility Disorders; Management of Ophthalmoplegia; Causes of Ophthalmoplegia*

Abbreviation

CCDDs: Congenital Cranial Dysinnervational Disorders; CPEO: Chronic Progressive External Ophthalmoplegia; EOM: Extra Ocular Muscles; TED: Thyroid Eye Disease; IIOD: Idiopathic Inflammatory Orbital Diseases; MRI: Magnetic Resonance Imaging; OMD: Ocular Motility Defects; ICP: Increased Intracranial Pressure; MDMA: 3, 4: Methylenedioxy-Methamphetamine; PCA: Posterior Cerebral Artery; MRA: Magnetic Resonance Angiography; CTA: Computed Tomography Angiography; CSF: Cerebrospinal Fluid; VDRL: Venereal Disease Reference Laboratory; ICHD: International Classification of Headache Disorders; CMV: Cytomegalovirus; SLSMDs: Single Large-Scale Mitochondrial DNA (mtDNA); OXPHOS: Oxidative Phosphorylation; PEO: Progressive External Ophthalmoplegia; MT: CYB-Mitochondrially Encoded Cytochrome B; KSS: Kearns Sayre Syndrome; AV: Atrio-Ventricular; RBBB: Right Bundle Branch Block; GNE-UDP-N: Acetylglucosamine 2-epimerase/N-Acetylmannosamine Kinase; IBMPFD: Inclusion Body Myopathy with Paget Disease of Bone; OPMD: Oculopharyngeal Muscular Dystrophy; OPDM: Oculopharyngodistal Myopathy; s- IBM: Sporadic Inclusion Body Myositis; PABPN1 gene: Poly (A) Binding Protein Nuclear 1; TK2: Thymidine Kinase 2; DGOUL: Deoxy Guanosine Kinase; POLG: Polymerase Gamma; SUCLA2: Succinyl Coenzyme A; dNTPs: Deoxy Nitro Phosphates; COX: Cyclooxygenase; RRM2B: Ribonucleoside-Diphosphate Reductase Subunit M2 B; CFEOM: Congenital Fibrosis of Extra Ocular Muscles; ROBO3: Roundabout Homolog 3; KIF21A: Kinesin Family Member 21A; HOXA1: Homeobox A1; PHOX2A: Paired Like Homeobox 2a; SALL4: Sal-Like Protein 4; LPS: Levator Palpebrae Superioris; TUBB3: Tubulin Beta 3 Class III; JMG: Juvenile Myasthenia Gravis; AChR: Acetylcholine Receptor; MuSK: Muscle-Specific Kinase; LRP4: Leucine Rich Protein 4; SFEMG: Single Fibre Electromyography; OMG: Ocular Myasthenia Gravis; MMF: Mycophenolate Mofetil; IVIG: Intravenous Immunoglobulin; RAPD: Rela-

tive Afferent Pupillary Defects; THS: Tolosa Hunt syndrome; NHL: Non-Hodgkin lymphomas; HL: Hodgkin Lymphomas; Nasopharyngeal carcinoma (NPC); EBV: Epstein Barr virus; CHOP: Cyclophosphamide, Hydroxy Daunomycin, Vincristine and Prednisone; MMI: Methimazole; MZ: Carbazole; PTU: Propylthiouracil; RAI: Radioactive iodine; CCF: Carotid-Cavernous Fistula; ECA: External Carotid Artery; INO: Internuclear Ophthalmoplegia

Introduction

Ophthalmoplegia or ophthalmoparesis is defined as paralysis or weakness of one or more extraocular muscles that are responsible for eye movements. It manifests with absence of ocular movements (referred to as jammed eyeballs) which may be active or passive, unilateral or bilateral, internal or external, total or partial, pupil sparing or pupil involving and painful or painless. It can be the presenting manifestation of a neurological, ophthalmological (myogenic or restrictive) or an endocrine disease and therefore assumes a great clinical relevance because of its unusual, complicated and clinically challenging manifestations and subsequent comprehensive multidisciplinary management approach. Treatment and prognosis depends on the underlying condition and should take into account the child's developmental needs, natural history of the condition, and side effect profiles of treatment options.

Etiology of ophthalmoplegia in paediatric age group can be multifactorial which includes the following broad categories:

1. Neurological causes
 - Supranuclear conditions
 - Infranuclear conditions
 - Combined Oculoparesis with both supranuclear and infranuclear mechanisms
 - Ophthalmoplegic migraine
2. Complicated Strabismus Syndromes like the congenital cranial dysinnervational disorders (CCDDs)
3. Myogenic causes
 - Chronic progressive external ophthalmoplegia (CPEO)
 - Kearns Sayre Syndrome
 - Muscular Dystrophies
4. Neuro-muscular junction anomalies
 - Myasthenia Gravis
 - Myasthenic syndromes
5. Orbital causes
 - Orbital Cysticercosis
 - Orbital tumours (tether the globe with the extra-ocular muscles (EOM))
 - Thyroid eye disease (TED)
 - Idiopathic inflammatory orbital diseases (IIOD), previously called pseudo-tumour.
6. Traumatic causes
 - Pediatric blow out fractures
 - Direct EOM injury
 - Nerve injury
 - Tethering of the EOM
 - Traumatic carotid cavernous fistula

General approach to a case of ophthalmoplegia requires comprehensive history regarding the age of onset of the symptoms to categorize the etiology as congenital or acquired. Details regarding onset, duration, progression, associated ocular symptoms and signs in the form of loss of vision, diplopia, eyelid signs like retraction, ptosis, edema, fatiguability, proptosis along-with associated systemic symptoms (headache, generalized aesthenia etc.) should be elicited, examined and documented. Clinical examination should include visual acuity assessment, pupillary examination, examination of ocular movements/ocular alignment/ocular position (presence of exophthalmos/enophthalmos) with a complete anterior segment and posterior segment evaluation. Ocular and orbital ultrasonography along-with imaging (Neuro-radio imaging) is performed which helps to localize, confirm and rule out the presence of the lesion. Contrast enhanced Magnetic resonance imaging (MRI) scans of the orbit and the head with specific directions regarding the particular tissue that is to be assessed, is advised which aids in a targeted management approach to the case of ocular motility disturbance.

Clinical Features, Diagnosis and Management

Adduction Deficiency Disorders

This is one of the most common causes of partial ophthalmoplegia in children and requires special mention. Causes include spasm of the near reflex, sixth nerve palsy, Duane's retraction syndrome and myasthenia gravis. This may manifest unilaterally or bilaterally and may not always be symptomatic in terms of presentation with diplopia.

a. Spasm of the Near Reflex

It's a triad of pupillary miosis (intermittent or continuous), increased accommodation and increased convergence. The subject is usually orthophoric or presents with a small, asymptomatic esophoria. Ocular motility defects (OMD) along with large esotropia may occasionally manifest especially in high myopia of about ~ 10 dioptre spherical [DS] [1]. A few patients may complain of blurry vision [2] or diplopia [1,2]. It can occur at any age but is most commonly observed between in young women of about 15 - 20 years [2]. Neurological conditions including Arnold Chiari malformations, neurofibroma of the posterior fossa, pituitary adenoma and vestibulopathy have been reported to be associated with accommodative spasm [3].

Management

Few patients may resolve spontaneously without any intervention (25%) [2]. Concave lenses (63% patients) may be used to relieve pseudomyopia and convex lenses have been used to inhibit excessive accommodation [1,2]. Cycloplegia with atropine (44% patients) or scopolamine, and patient reassurance are other treatment options apart from adaptations including face turn (13%) or head tilt (13%) [1,2].

b. Sixth nerve palsy

Abducens nerve palsy, congenital or acquired, is the most common cranial nerve palsy in paediatric patients at birth. It has been observed in 0.1% cases of vaginal delivery, 2.4% of forceps assisted delivery and 3.2% of vacuum extracted deliveries [4]. Sixth nerve palsy presents with abduction deficit, unlike what is observed in accommodative spasm, where they are normal.

Patients with congenital sixth nerve palsies are usually asymptomatic unlike those with acquired palsies who manifest with diplopia, more at distances than at near, as also a head turn away from the palsied muscle (Figure 1) [5]. Up to 20% of sixth nerve palsies are bilateral [4]. Acquired palsies are more serious, as their presence may indicate a neoplasm [4-6]. Table 1 summarises the various etiologist of sixth nerve palsies in children.



Figure 1: 1A: 8-year old female with acute onset right sixth nerve palsy showing limitation in abduction of the right eye.

Holmes., et al (1999) [6]
Undetermined 36%
Trauma 27%
Post viral 18%
Tumor resection 18%
Congenital 8%

Table 1: Etiology of sixth nerve palsy in children.

Early stages of metastatic neuroblastoma and pontine gliomas can present as isolated unilateral or bilateral sixth nerve palsy in children between 3 to 6 years of age and can have concomitant seventh nerve involvement [7]. Additional symptoms may include headaches, nausea, diplopia, stiff neck, vomiting and difficulties with gait [7]. According to one study, 60% of children under the age of 11 with increased intracranial pressure (ICP) also exhibited sixth nerve palsies. Acquired lateral rectus palsies have been reported following viruses, specifically varicella, and infections, such as meningitis and Lyme disease [5,6]. These palsies generally resolve within 2 - 4 months [5,6]. Gardening’s syndrome, 3,4-methylenedioxy-methamphetamine (MDMA - Ecstasy) abuse, tumours and aneurysms in petrous apex area can produce sixth nerve involvement [4]. Bilateral sixth nerve palsies may be confused with congenital esotropia and examining for the “dolls eye response” can help differentiate the two conditions. In congenital esotropia, passive dolls eye movements are full unlike that in sixth nerve palsy.

Management

Monitoring patients with sixth nerve palsy every two to six weeks for improvement is recommended and timely referral if the symptoms worsen or do not improve in six months is advocated [4]. Lee., et al. recommend neuroimaging immediately if papilledema or other neurological signs are present, and within one week in all other cases.

In patients with chronic sixth nerve palsies lasting longer than 6 months where no progressive cause can be elicited, possible treatment options include observation, surgery or Botox injections.

c. Duane's Retraction Syndrome (DRS)

Classified as congenital cranial dysinnervation syndrome (CCDD), this is one of the most common causes of abduction deficit. Huber type I DRS is associated with marked limitation of abduction with minimally defective or normal adduction, globe retraction and palpebral fissure narrowing in adduction, widening in abduction. It is the most common form of DRS that presents at an early age. Huber type II presents with marked limitation of adduction with primary position exotropia of the affected eye, abduction is normal or slightly limited with globe retraction and palpebral fissure narrowing in attempted abduction is observed. It is the least common presentation. Type III DRS manifests with limitation or complete absence of adduction and abduction with globe retraction and palpebral fissure narrowing in attempted adduction. Classification of DRS based on primary position deviation as esotropic, exotropic or orthotropic is clinically more relevant than Huber's classification prior to deciding for surgical intervention in these patients (Figure 2A and 2B) [4,7]. The exact cause of this anomaly is not known however, studies have suggested agenesis of the sixth nerve, which results in a mis-wiring of the third cranial nerve to the lateral rectus muscle. Women are usually affected more frequently than men, the left eye more frequently than the right with 10% having a positive family history, and 15 - 20% cases being bilateral [8]. Goldenhar's syndrome and Klippel-Feil syndrome are amongst the systemic associations [8].



Figure 1: 2A: Globe retraction and palpebral fissure narrowing in the right eye with limited abduction in the left eye in a child with bilateral Duane retraction syndrome. 2B- Globe retraction and palpebral fissure narrowing in the left eye with limited abduction in the right eye in a child with bilateral Duane retraction syndrome.

Management

In patients with strabismus, there is often deep suppression [8]. In symptomatic patient's complaints relate to poor binocular fusion and can include intermittent diplopia, fatigue and eyestrain with near tasks [8]. Refractive correction and amblyopia management should be the primary focus of treatment. Surgical correction is warranted in cases with significant esotropia, marked head posture, upshoot or downshoot in adduction or very marked palpebral aperture retraction [8].

Cranial nerve palsy

a. Third nerve palsy

Isolated, persistent third nerve palsy in a child is mostly congenital, associated with aplasia or abnormal development of the structures of the ocular motor nucleus due to an *in utero* insult [9]. Clinically the child presents with ptosis, miosis (due to anomalous sphincter innervation) and extra-ocular motility deficits (Figure 3A and 3B). Cavernous sinus lesions, neoplasms of the base of the skull, carcinomatous meningitis, infections, sinus mucocoeles and inflammatory conditions can present with multiple cranial nerve involvement.



Figure 3: 3A: A 15-year-old boy with ptosis, exodeviation and hypodeviation OD due to congenital third nerve palsy; 3B: The child can take up fixation with the right eye, thus indicating good vision in that eye. The normal eye manifests exotropia (secondary deviation).

Appropriate investigative approach to a patient with third nerve palsy depends on the age of the patient and pupillary reactions. Pupil involving third nerve palsy needs neuroimaging to rule out posterior cerebral artery (PCA) aneurysm. Magnetic resonance angiography (MRA) and computed tomography angiography (CTA) are useful, but the exact sensitivity and availability of these tests vary. A catheter angiogram helps pick up small aneurysms that may be missed on non-invasive imaging studies. In cases of evolving acute third nerve palsy due to aneurysm, development of mydriasis warrants urgent imaging. Muscle entrapment due to fracture of the orbital wall can also be seen on imaging. Serology for Lyme disease, syphilis, and ESR to exclude temporal arteritis, cerebrospinal fluid (CSF) analysis including cell counts, protein, glucose, cytology, and Lyme and Venereal Disease Reference Laboratory (VDRL) titres may be done in cases where imaging is inconclusive.

Management

Diplopia resulting from acute third nerve palsy needs monocular patching/occlusion or prisms. A stable ocular misalignment for 6 to 12 months can be surgically corrected. Complete third nerve palsy presents with a significant incomitance in the deviation in horizontal and vertical planes wherein surgery aims to establish single binocular vision in the primary position [10].

Supra-maximal lateral rectus recession can correct manifest exotropia with or without a medial rectus resection [10]. Transposition of the horizontal muscles to facilitate vertical eye movements and transposition of the superior oblique tendon to create an adducting force are other possible procedures [11]. A posterior fixation suture on the contralateral yoke muscle creates a mild limitation of eye movement without affecting primary position [18]. Partial third nerve palsy causing isolated impairment of elevation or depression may benefit from resection of the involved vertical muscle combined with an adjustable recession (or posterior fixation suture) of the contralateral yoke muscle, producing an improved field of single binocular vision [11]. Ptosis correction if done, follows squint correction. However, amblyopia management is the foremost aim of dealing with congenital third nerve palsies.

b. Congenital fourth nerve palsy

Congenital fourth nerve palsy is usually accompanied with hypoplasia of the fourth nerve nucleus, birth trauma, anomalous muscle insertion, structural abnormalities of the tendon, or inferior oblique muscle abnormalities [12]. Midbrain haemorrhage, infarction, or demyelination, schwannoma, aneurysmal compression, meningitis, hydrocephalus, and herpes zoster ophthalmicus, neoplastic processes are other possible etiologies [13]. Inferior oblique overaction, large vertical fusional amplitude can be observed, and the latter may decompensate later in life causing symptomatic diplopia. A lesion leading to the involvement of fourth nerve nucleus or proximal fascicle may cause contralateral superior oblique weakness in association with ipsilateral Horner syndrome, ipsilateral internuclear ophthalmoplegia or contralateral relative afferent pupillary defect without visual loss.

Management

Occlusion of the affected eye and/or base down prisms can provide temporary relief when spontaneous recovery is anticipated [14]. Prisms are generally effective for patients with congenital palsies because they have large fusional amplitudes [14]. However, torsional diplopia remains uncorrected by prisms, and may limit the patient's satisfaction. Persistent symptomatic fourth nerve palsies with stable deviation can be corrected surgically when conservative measures fail.

c. Ophthalmoplegic migraine

Ophthalmoplegic cranial neuropathy is a rare neurologic syndrome characterized by recurrent bouts of headache and ophthalmoplegia. Patients may present with mydriasis and ptosis subsequent to third cranial nerve involvement. The condition usually manifests in children but can persist in adulthood [15]. Most patients recover spontaneously. However, a few may have residual neurologic deficits. Transient visual phenomena before, during, or after the onset of headache distinguishes the condition from migraine [16].

The second edition of the International Classification of Headache Disorders (ICHD) defines ophthalmoplegic migraine as at least 2 attacks characterized by a "migraine-like" headache followed within 4 days by paresis of the third, fourth, and/or sixth cranial nerves, including ophthalmoparesis, ptosis, or mydriasis [16]. Tumour, infection, and thrombosis presenting with painful ophthalmoparesis must be excluded by appropriate imaging [17]. While the pathophysiology of ophthalmoplegic migraine is unclear, studies have revealed no evidence to suggest a systemic inflammatory process associated with ophthalmoplegic migraine [18]. Inflammatory cerebrospinal fluid abnormalities were reported in only 2 cases with fourth nerve involvement: one with an elevated IgG index, without oligoclonal bands and the other with a single oligoclonal band unlike no intrathecal inflammation in patients with third nerve palsy pointing to etiopathogenetic differences in ophthalmoplegic migraine, involving the fourth nerve [16]. A case report highlights viral (Cytomegalovirus {CMV}) illness leading to manifestation of this clinical entity [19]. Familial cases with recurrent bouts of facial palsy have been reported pointing to association with neurotropic viruses like herpes simplex and varicella zoster virus [20].

Cases with third nerve involvement also show nerve enhancement on gadolinium enhanced MRI which usually does not enhance normally [17]. A recurrent demyelinating cranial neuropathy for ophthalmoplegic migraine is recently accepted theory for this entity, with some authors suggesting nerve swelling seen in chronic inflammatory demyelinating poly-radiculopathy as a pathological mechanism [15].

Management

No published treatment trials for ophthalmoplegic migraine are available. However, oral steroids may be of possible benefit in treating acute exacerbations [16]. Botulinum toxin injection or strabismus surgery may be considered for patients with persistent eye misalignment [21]. More studies are required to fully understand the etiopathogenesis and management recommendations of this neurological entity.

d. Single large-scale mitochondrial DNA (mtDNA) deletions (SLSMDs)

The frequency of occurrence of SLSMDs exceeds any other mitochondrial DNA disorders in paediatric age group [22]. The etio-pathogenesis and the natural history of this disease needs further understanding, however defective mitochondrial oxidative phosphorylation (OXPHOS) function has been noted in these patients [22].

e. Pearson Syndrome

This is a disorder which presents with sideroblastic anemia, dysfunction of the exocrine part of pancreas, myogenic and neurological impairment, fibrosis of the pancreas that manifests with insulin-dependent diabetes, failure to thrive and eventually resulting in early death [23]. Majority patients die in infancy, are often have low birth weight and survivors often develop symptoms suggestive of Kearns-Sayre syndrome [23]. Neuromuscular symptoms account for high mortality rates in patients without haematological involvement [22]. Brain MRI abnormalities included basal ganglia and white matter lesions. Renal manifestations of the syndrome include glomerular compromise, renal tubulopathy, fanconi type tubulopathy, nephrocalcinosis and end-stage renal failure [22]. Children with age past 1 year presenting with recent onset ptosis should undergo screening for SLSMDs. Deletion of the MT-CYB gene correlates with more severe phenotype [22].

f. Kearns Sayre Syndrome (KSS)

KSS is a mitochondrial deletion disorder presenting before 20 years of age characterised by progressive external ophthalmoplegia with ptosis, pigmentary retinopathy, heart block, cerebellar syndrome, or cerebrospinal fluid protein > 100 mg/dl [24]. Patients may present with dementia, sensorineural hearing loss, and multiple endocrine abnormalities, including short stature, diabetes mellitus and hypothyroidism [25]. Cardiac involvement, affecting nearly 60% of the patients, manifesting as progressive degeneration of the myocardial conducting system is the most important prognostic factor [25]. Third degree atrio-ventricular (AV) block, complete and incomplete right bundle branch blocks (RBBB), fascicular blocks, and nonspecific intraventricular conduction delays have all been seen on electrocardiogram.

Management

Pacemaker implantation is advocated in patients with significant delay in conducting system of the heart. Asymptomatic RBBB needs 3 - 6 monthly ECG monitoring with a regular cardiological follow-up.

Patients with multisystem involvement are increasingly being investigated for possibility of mitochondrial disorders and most of these patients require symptomatic support. Due to associated hormonal imbalances, endocrinology monitoring is recommended and appropriate hormonal supplementation in the form of thyroxine, insulin, Vitamin D and growth hormone may be needed [22]. Patients with impaired pancreatic exocrine function require pancreatic enzyme replacement [22]. Regular audiometry is required in patients with sensorineural hearing loss and may need audiometric rehabilitation in the form of hearing aids or cochlear implantation [22]. Visual field

charting should be performed in cooperative children presenting with pigmentary retinopathies including retinitis pigmentosa. Coordinated involvement of audiology specialists, cardiologists, endocrinologists, gastroenterologists, haematologists, nephrologists, neurologists and ophthalmologists is need for overall management of children with SLSMDs.

g. Oculopharyngeal dystrophy

Myopathy with rimmed vacuoles represents a group of heterogenous muscle disorders that manifests with progressive muscle weakness. These disorders have comparable histopathological features on muscle biopsy but have variable clinical manifestations [26]. Hereditary myopathies and acquired myopathies, such as GNE myopathy where GNE is an abbreviation for the mutated gene (UDP-N-acetylglucosamine 2-epimerase/N-acetylmannosamine kinase), inclusion body myopathy with Paget disease of bone (IBMPFD) [27], frontotemporal dementia, oculopharyngeal muscular dystrophy (OPMD) [28], oculopharyngodistal myopathy (OPDM) [29], sporadic inclusion body myositis (s-IBM) [26] are the disorders included in this group. OPMD manifests with limb weakness and oculopharyngeal muscle weakness that occurs as result of abnormal (GCG)_n expansions of the first exon in *PABPN1* gene [30]. This dystrophy is commonly observed in patients more than the age of 50 year. However, it may manifest in younger patients in the adolescent age group as well. The disorder has both autosomal dominant and autosomal recessive inheritance pattern although the causative gene of OPDM is still not unknown. Patients present with external ophthalmoplegia, pharyngeal muscle weakness, and distal muscle weakness. Affected individuals rarely present with deafness or visual impairment.

Mitochondrial DNA depletion syndrome

a. Thymidine Kinase2 (Tk2) related Mitochondrial DNA depletion syndrome

Tk2 related mitochondrial disease are a clinically heterogenous group of autosomal recessive disorders described in 1991 with an onset in early infancy or childhood presenting with decreased number of mitochondrial DNA copies in affected tissues limiting the synthesis of mtDNA-encoded respiratory chain components [31]. The incidence varies between 1: 5,000 and 1: 10,000 live births [32]. Thymidine kinase 2 (TK2)- associated with the myopathic form of the disease, deoxyguanosine kinase (DGUOK)- linked with the hepatocerebral form, polymerase gamma (POLG)- hepatocerebral form, more importantly with Alper's syndrome, and *SUCLA2*, the gene encoding the β -subunit of the adenosine diphosphate-forming succinyl coenzyme A synthetase ligase- responsible for encephalomyopathic form; are the four genes that have an integral role in deoxyribonucleotide triphosphate metabolism [33]. Till date 50 individuals have been reported to be affected with the disease [34].

TK2 gene is an intramitochondrial pyrimidine nucleoside kinase that lies on chromosome 16q22, encodes thymidine kinase (TK2) that phosphorylates dNTPs, such as deoxythymidine, deoxycytidine and deoxyuridine involved in the salvage pathway of deoxynucleotide synthesis [35]. Active transport of cytosolic dNTP's and salvage pathways give rise to mitochondrial dNTP's which are responsible for replication of mtDNA since mitochondrion is unable to synthesize dNTP's de novo [35]. Primary site of involvement is the muscular tissue with variable to no effect on liver, brain, heart or skin. The disorder presents with a mild disease to a severe, rapidly progressing myopathy of infantile or childhood onset which may lead to respiratory failure and death. Basal TK2 activity is very low in human muscle tissue compared to liver or heart and low TK2/COX and TK2/mtDNA ratios are observed in muscle which could also contribute to the vulnerability of skeletal muscle to TK2 deficiency [36]. Development is usually normal early in life, but with progressive muscle weakness impairment in motor skills such as standing, walking, eating, and talking develop. Weakness in the muscles that control eye movement leads to drooping of the eyelids manifesting as progressive external ophthalmoplegia which may be a manifestation [35].

b. *RRM2B* -related mitochondrial DNA depletion syndrome

This gene is located on chromosome 8q23.1 and codes for the small subunit of a heterotetrametric enzyme p53-inducible ribonucleotide reductase responsible for de novo conversion of ribonucleotide diphosphates into their corresponding deoxyribonucleoside diphosphates which are essential for DNA synthesis [37]. The key function of the enzyme is in maintaining the mitochondrial dNTP pools for mtDNA synthesis. Mutations in this gene result in neonatal hypotonia, lactic acidosis, failure to thrive, psychomotor delay, sensorineural hearing loss tubulopathy and eventually death after a few months of onset of the disease [37]. Chronic progressive external ophthalmoplegia with multiple mtDNA deletions along-with mild to moderate ptosis has been described as a phenotypic variant of this group of mitochondrial DNA depletion disorders. Extra-ocular neurologic complications are common in adults with genetically confirmed *RRM2B*-related mitochondrial disease.

Congenital fibrosis of extra ocular muscles (CFEOM)

The concept of “Congenital fibrosis of the extra-ocular muscles” (CFEOM) was proposed after it was observed that many children with disorders of ocular motility at birth had fibrotic extra-ocular muscles suggesting a myogenic pathology [38]. A paradigm shift in the opinion relating to etio-pathogenesis was emphasized and a neurogenic and genetic basis was purported for these disorders presently termed as the “congenital cranial dysinnervation disorders.”

Mutations in genes required for correct axonal targeting of the motor neurons (*ROBO3*), motor neuron development (*HOXA1*, *PHOX2A*, and likely *SALL4*), and correct axonal targeting of the extra ocular muscles (*KIF21A*) result in these group of ocular motility disorders namely CCDD's [39].

a. CFEOM1

This variant of CFEOM manifests with congenital non-progressive bilateral external ophthalmoplegia, where both eyes are infraducted with limited elevation, congenital bilateral ptosis and spared pupillary reflex [40]. High-resolution MRI of the brainstem and orbit reveal absence of the superior division of the oculomotor nerve (CNIII) and the corresponding motor neurons in the midbrain oculomotor nucleus with significant abnormalities of the levator palpebrae superioris (LPS) and SR muscles [41]. These findings suggest that *FEOM1* locus, mapped to centromeric region of chromosome 12 is of prime importance in the development of superior division of the oculomotor nerve and is likely important for axonal targeting of the extraocular muscles [42]. *KIF21A* (Developmental kinesin) gene structurally resembles classical kinesin with three domains namely motor, stalk, and tail (which carries an unknown cargo and interaction between these three domains) result in homo- or heterodimerization. Heterozygous mutations in this gene in patients with *CFEOM1* inhibit dimerization of *KIF21A* to itself or another binding partner or may interfere with the ability of *KIF21A* to move into and out of an active state resulting in inhibition of *KIF21A* to deliver its unidentified moiety that it carries from the oculomotor neurons to the synapse of the developing neuromuscular junction of the extra-ocular muscle [43].

b. CFEOM2

This is an autosomal recessive syndrome characterised by bilateral ptosis and absent adduction, up gaze, and down gaze mimicking bilateral third nerve palsies resulting from aberrant axonal targeting of the extraocular muscles by a branch of the oculomotor nerve [44]. Abduction is incomplete with anisocoria and absent pupillary light reflex with preserved reactions to drugs [45]. Bilaterally absent third nerves are observed on MRI [43]. Genotypically, homozygous loss-of-function mutations in the *PHOX2A* gene (previously termed ARIX, also identified in an Iranian pedigree), [45] a homeodomain transcription factor that is prominently expressed in developing oculomotor and trochlear motor neurons nearly indispensable for their survival. Linkage analysis mapped CFEOM2 to chromosome 11q13, referred to as the *FEOM2* locus.

c. CFEOM3

CFEOM3 is an autosomal dominant disorder with clinical manifestations similar to CFEOM1 except for retained ability to elevate the eyes above midline in a few cases. Heterozygous mutations in at least two genes, TUBB3 (CFEOM3A), a component of microtubules [46] and rarely KIF21A (CFEOM3B) have been found to be mutated in these cases. Facial palsy, peripheral neuropathy, wrist and finger contractures, and intellectual, social, and behavioural impairments are amongst the other manifestations of this variant of CFEOM [47]. Corpus callosum and anterior commissure dysgenesis have been reported on neuroimaging. A CFEOM3C variant has been described wherein a reciprocal translocation in chromosome 2q and 13q have been documented in 3 subsequent generations of a family [47].

Management

Large recessions with/without adjustable suture technique, resections, tenotomies, myectomies, fixation of a muscle to the orbital wall, and botulinum toxin injection are the surgical modalities for managing CCDD's [48]. Resections are generally avoided, in the management of CFEOM. The need for multiple surgical procedures should be clearly explained to the patients emphasizing the under-correction after single surgical procedure and early surgery should be considered in adults in view of more tight and friable muscle in this group of patients unlike paediatric age group [48].

Juvenile Myasthenia gravis (JMG)

Myasthenia gravis (MG) is an autoimmune disease resulting in muscular weakness and easy fatigability wherein antibodies are directed at the postsynaptic membrane of the neuromuscular junction. Juvenile myasthenia gravis (JMG) is defined as myasthenia which presents in children less than 19 years of age. Antibodies to the nicotinic acetylcholine receptor (AChR) are observed most commonly in the affected individuals which are relatively less frequently demonstrated in prepubertal patients unlike higher titres in adolescent and adult patients [49]. Seronegative patients have shown to demonstrate antibodies to muscle-specific kinase (MuSK) and to Leucine rich protein 4 (LRP4). Placental transfer of maternal AChR (or very rarely MuSK antibodies) to infants of mothers with autoimmune MG results in transient neonatal myasthenia [50]. The affected baby is normal at birth later manifesting with hypotonia, weak cry, poor suck, reduced movements, ptosis and facial weakness, and occasional respiratory insufficiency requiring mechanical ventilation and may benefit from anticholinesterases.

JMG is more common in oriental than in Caucasian populations and nearly 50% of all cases of ocular MG in Chinese populations present in childhood. Peak age at presentation is 5 - 10 years [51]. Ptosis is the most common manifestation (Figure 4) along-with unilateral or asymmetric ophthalmoplegia, strabismus, and lid twitch after sustained upgazed. This may lead to dense amblyopia. Generalised muscle weakness leads to painless fatigability of the bulbar and limb musculature, with subsequent dysphonia, dysphagia, and proximal limb weakness. Weakness usually becomes more at the end of the day and improves with rest. Frequent chest infections may necessitate ventilatory support which is termed as "myasthenic" crisis. Pre-pubertal JMG predominantly presents as ocular myasthenia, with an equal male to female ratio unlike peri-/post-pubertal children wherein females are affected more than males. Case series in children have reported lower rates of generalisation than in adults.



Figure 3: Bilateral severe ptosis with frontalis overaction in a 4-year-old child with myasthenia gravis.

Congenital myasthenic syndrome is usually inherited as an autosomal recessive disorder, present in the first years of life often with a positive family history, and needs electrophysiology, DNA analysis and muscle biopsy in few cases to establish diagnosis [51]. Children who are seronegative for AChR may have antibodies to MuSK and these patients with MG represent a distinct subgroup of JMG with a marked female predominance, with more severe manifestations in the form of respiratory compromise associated with facial and bulbar weakness. Post thymectomy for AChR seropositive MG, a few patients may develop MuSK antibodies referred to as seroconversion not known in adults [52]. The edrophonium test using a fast-acting, short duration cholinesterase inhibitor aids in diagnosis of the condition [50]. Single fibre EMG (SFEMG) is of benefit in diagnosis of seronegative MG and congenital myasthenic syndromes [53]. Repetitive nerve stimulation in JMG will show a decrease in the compound motor action potential of > 10% by the 4th or 5th stimulation [53]. The procedure can be performed under local or even general anaesthesia. A normal result makes the diagnosis of myasthenia very unlikely due to high sensitivity of the test [53]. Thymus is not commonly involved in the pathogenesis in MuSK positive disease [80]. Thymus hyperplasia is the most common abnormality of the thymus in JMG. However, thymoma is particularly rare in prepubertal children.

Management

Higher rates of remission are observed in affected patients with JMG (predominantly children) than adults. Children who have not attained puberty have the highest rates of spontaneous remission. Multidisciplinary management involving a paediatrician with assistance from a paediatric neurologist, physiotherapist, occupational therapist, psychologist, speech therapist and dietician are all required for comprehensive treatment of these children. There are few studies suggesting interventions in children with MG, particularly prepubertal children. Acetylcholinesterase inhibitors, with long acting agents like pyridostigmine 4-6 times a day, are amongst the first-line treatment in JMG and provide symptomatic relief. Cautious use in MuSK-positive children is advocated considering a risk of acetylcholine hypersensitivity [54].

Thymectomy may remove thymic germinal centres and increases the probability of remission or improvement of symptoms in AChR seropositive, non-thymomatous, autoimmune MG, as concluded in the systematic reviews [55]. Risk of immunosuppression must be kept into consideration after thymectomy. It is not recommended in MuSK-positive disease and its role in pure ocular myasthenia gravis (OMG) remains controversial, who require long term immunosuppression. Reduction in the risk of progression of OMG to generalised JMG post thymectomy remains unsettled.

Corticosteroids are the first line agents for medical management but can worsen symptoms in the first few weeks of use, particularly if started at high doses [56]. Early use of steroids may decrease progression of ocular to generalized myasthenia gravis but the decision to use steroids should be considered early in the course of patients diagnosed with ocular myasthenia gravis [57]. Combination therapy with a steroid-sparing immunosuppressant like azathioprine is advisable in view of long term side effects of steroid therapy, more so in children leading to growth failure, predisposition to severe infection, and delay in receiving live vaccination [56].

Azathioprine has been found to be effective as a single agent used commonly with prednisolone as a steroid-sparing agent. Azathioprine or corticosteroids may reduce the progression of ocular myasthenia gravis to the generalised form of disease [58]. A Cochrane review suggests that cyclosporin either as monotherapy or with corticosteroids, or cyclophosphamide in combination with corticosteroids, improves symptoms of MG within 1 year [59]. Mycophenolate mofetil (MMF) when used either as monotherapy or in conjunction with prednisolone has shown benefit as per a recent retrospective study [60]. It may take one year of treatment to show improvement. Tacrolimus, interleukin 2 inhibitor and Rituximab, a chimeric IgG monoclonal antibody that depletes B cells, have been used in JMG as well with rituximab showing promising results in refractory JMG [61]. Improvement in symptoms after plasma exchange or administration of Intravenous Immunoglobulin (IVIg) is usually temporary and is largely reserved to optimise condition for surgery before thymectomy and in management of myasthenic crisis [62].

Orbital inflammation

a. Orbital cellulitis

Orbital or post-septal involvement can cause visual and life-threatening complications and needs to be distinguished from preseptal cellulitis. Orbital cellulitis presents with erythematous eyelid swelling, ophthalmoplegia, proptosis, fever, ptosis, headache, pain, drowsiness, leucocytosis, chemosis, blurred vision and relative afferent pupillary defects (RAPD). However, clinical signs of the disease may be absent in a vast majority of children less than 3 years of age wherein it may be difficult to assess the post-septal involvement as the lids may approximate closely due to significant swelling. Imaging (high resolution orbital CT scan) and elevated C- reactive protein levels are other ways to distinguish orbital from pre-septal cellulitis [63]. Idiopathic orbital inflammatory disease, thyroid ophthalmopathy, neoplasm, sarcoidosis, rheumatologic disease like Wegener's granulomatosis, polyarteritis nodosum, and giant cell arteritis are important differentials for orbital inflammatory disease. A sub-periosteal abscess presents with non-axial proptosis and limitation of extra-ocular movements towards the abscess. An intraorbital abscess is extremely uncommon and may cause visual compromise if present within the muscle cone as it may cause optic nerve compression. A study reported 6.9% lid abscess in children with preseptal cellulitis increasing to 10% in orbital cellulitis [64]. Another study reported that patients presenting with ophthalmoplegia, protrusion of the eyeball, variably severe periorbital edema and a peripheral blood neutrophil count $> 10,000/\mu\text{L}$ are considered high risk features for developing abscess. Such patients will benefit from emergent MRI [65]. Dermatologic infection are an important etiological factor in 7% children with orbital cellulitis, however, Liu, *et al.* reported it as the most common (19.4%) in their series [25].

Management

Medical and surgical therapy may both be needed in patients presenting with orbital cellulitis. Aggressive antibiotic therapy with goal directed management of the underlying predisposing factors is the aim. Surgical intervention is indicated in cases of orbital cellulitis with an associated foreign body and abscess [66]. Broad spectrum antibiotic covering both gram positive and gram-negative bacteria with anaerobic therapy may be initiated primarily until the results of microbiological blood and pus culture and sensitivity are available. Use of corticosteroids in children with orbital cellulitis remains controversial although it may be added to control associated inflammation [64]. Surgery is indicated for nonspecific abscess if orbital signs and/or symptoms do not resolve and progress after 48 hours of adequate antibiotic therapy [64,66]. Oral antibiotic should be continued for 1 - 2 weeks following a course of intravenous antibiotic. Parenteral antibiotic for at least 1 week, before switching to oral therapy to complete a 3-weeks course has been suggested by few authors.

b. Pediatric Tolosa Hunt syndrome (THS)

It is an uncommon disorder of the pediatric age group characterized by unilateral painful ophthalmoplegia typically presenting with a relapsing-remitting course. The disorder responds well to corticosteroid treatment. Documentation of granulomatous inflammation on neuroimaging or histopathology is essential to establish a diagnosis of THS, which essentially is a diagnosis of exclusion. Revised International Headache Society criteria for diagnosis of THS incorporates one or more episodes of one sided orbital pain, persisting for weeks if not treated, painful paresis of one or more of the third, fourth, and/or sixth cranial nerves and/or demonstration of granuloma by MRI or biopsy, pain which either coincides with the onset of paresis or precedes it by not more than 2 weeks and resolves within 72 hours of starting treatment with corticosteroids [67]. Differential diagnosis of painful ophthalmoplegia include neoplasms, aneurysms, diabetic cranial neuropathy, ophthalmoplegic migraine, orbital pseudotumor, intracranial vasculitis, basal meningitis, and cavernous sinus thrombosis.

Management

Literature is scarce on the use of steroids in the management of THS along-with their dosage schedules. Dexamethasone in a dose of 1 mg/ kg/day selectively reduced orbital pain, however high-dose prednisolone therapy (2 mg/kg/day), resulted in complete resolution of all THS symptoms [67]. Cranial nerves paresis takes around 3 days to normalise in children unlike 2 to 8 weeks in adults [67]. It is proposed that high dose steroids are more likely to be effective than lower doses in THS patients as far as resolution of symptoms and avoidance of recurrences is concerned with repeated neuroimaging, which helps overcome diagnostic dilemmas [68]. A significant response to infliximab has been reported by O'Connor and Hutchinson in a female with THS [69]. Initial neuroimaging can be normal in subacute forms of THS, and a diagnostic algorithm for therapeutic management in children with THS is required relating to the drugs, their dosage schedule and role of steroids in management.

c. Orbital cysticercosis

Cysticercosis in the orbit is noted commonly in children and young adults and should be considered as a differential diagnosis in patients with orbital dermoid. History of exposure on a visit to endemic area with the presence of subcutaneous nodules helps suspect the diagnosis of cysticercosis. Cysticercus larva involves the posterior segment via posterior ciliary artery and enters the sub-retinal space and finally into the vitreous humor as a freely floating cyst. Eye involvement is noticed in the form of orbital intraocular, sub-retinal, and optic nerve lesions [70]. Symptoms of neurological illness along-with increased intracranial pressure points to a CNS involvement with the cysticercosis larva. Surgically accessible cysts can be seen in superficial anterior orbit, subcutaneous tissues of the eyelid, or conjunctiva. Limitation of ocular motility is suggestive of myocysticercosis which is the commonest form of cysticercosis in the orbit.

Management

Treatment consists of antihelminthic namely albendazole along-with corticosteroids [71]. Corticosteroid cover is important for the suppression of the acute inflammatory reaction which may follow on the death of the parasite and cyst rupture. Orbital imaging may itself establish the diagnosis of cysticercosis apart from serum antibody levels. Calcifications and fibrosis are better appreciated on CT scan and orbital MRI helps identify a live cyst. Cyst removal should be done with caution and leakage of the contents should be avoided. Absolute alcohol injection into the cyst may kill the organism in cases not suited for albendazole [71].

Pediatric head and neck malignancies

Childhood cancer is second only to accidental trauma as a cause of death in children more than 5 years of age. Head and neck are involved in 12% of all childhood malignancies. Of note amongst pediatric head and neck malignancies are non-Hodgkin lymphomas (NHL), Hodgkin lymphomas (HL), rhabdomyosarcomas, thyroid malignancies, nasopharyngeal carcinomas (NPC), salivary gland malignancies, and neuroblastomas.

a. Nasopharyngeal carcinoma (NPC)

Median age of NPC development is 13 years and shows male preponderance [72]. Factors related pathogenetically to NPC include HLA subtypes, environmental factors like eating salted fish, nitrosamine exposure and Epstein Barr virus (EBV) infection [72]. As per WHO classification of NPC, the suggested types comprise Type I (keratinizing squamous cell carcinoma), type II (nonkeratinizing carcinoma), and type III (undifferentiated carcinoma) [72]. Clinically the patient may present with a mass in the upper neck which is usually painless and nasal obstruction may lead to diagnostic confusion with chronic rhinitis associated with episodic epistaxis, otalgia, and conductive hearing loss. Extension into the skull base and involvement of sixth cranial nerve VI, causes weakness of lateral gaze and diplopia. In addition, other cranial nerves like the IIIrd, IVth, Vth, IXth to XIIth may also be involved.

Management

Investigations for NPC include diagnostic biopsy, CT and/or MRI of the primary site, computerised tomography of the chest, abdominal ultrasound, and bone marrow biopsy for metastasis screening. EBV titres correlate with the disease severity and titres need to be assessed. High-dose radiotherapy to the nasopharynx and involved neck lymph nodes is suggested treatment modality as in adults [73]. In view of co-morbidity associated with radiation exposure, trials of adjuvant, neo-adjuvant, and concomitant chemotherapy are done. Maxillary swing procedure is not recommended as a management option in view of skeletal immaturity, surgical morbidity, and concern about incomplete resection [73].

b. Rhabdomyosarcoma

Rhabdomyosarcoma is the most common soft tissue sarcoma in children and adolescents and more than one-third of cases present in the head and neck region [74]. It is a malignant tumor of mesenchymal origin. The most common form is embryonal with its spindle cell and botryoid variants and its incidence declines with age, and the alveolar form peaks in childhood and adolescence [75]. It may present with an orbital mass which most often is asymptomatic or may present with ophthalmoplegia and proptosis and requires a needle or a core needle biopsy for adequate tissue diagnosis on histopathologic and molecular examination. Imaging is conducted and the tumor is staged based on its size, location, extent of involvement, and the absence or presence of metastases following which a multidisciplinary approach is needed consisting of chemotherapy and either surgery or radiotherapy.

c. Neuroblastoma

This tumor is the most common extracranial solid tumor of childhood. Origin is from the neural crest progenitor cells of the sympathetic nervous system and may present as a lateral neck mass causing compression of the neurovascular bundle of the neck and with varied clinical manifestations including Horner's syndrome. Metastatic spread to the orbital soft tissues can present with periorbital swelling, ecchymosis, or ophthalmoplegia. After a comprehensive systemic and ocular workup including imaging, to assess extent of the tumor, decision for treatment is taken comprising of surgery, with or without adjuvant chemotherapy, and infrequently radiotherapy which depends on the clinical stage of the disease.

d. Lymphomas-Non-Hodgkin's and Hodgkin's lymphoma

Non-Hodgkin's lymphoma (NHL) in children is not very uncommon and is seen in around 25% of children aged less than 10 years and has male predilection [76]. Three types of NHL are observed histologically namely low, intermediate, and high-grade varieties with high grade mature B cell type (Burkitt's (40%), diffuse large B cell type (10%) type being most common in children [77]. Hepatosplenomegaly, unilateral cervical lymphadenopathy and night sweats can be presenting features along-with proptosis and ophthalmoparesis in some patients. The commonly used agents for chemotherapy include CHOP-based regimens (cyclophosphamide, hydroxy daunomycin, vincristine, and prednisone) and radiotherapy is used in central nervous system (CNS) prophylaxis in the event of suspected involvement.

Classical' Hodgkin's lymphoma (90%), comprising lymphocyte-depleted (rare in children), nodular sclerosing, and mixed cellularity subtypes, and 'lymphocyte-predominant' Hodgkin's lymphoma (10%) are two main categories of Hodgkin's lymphoma. Classical Hodgkin's lymphoma has characteristic CD15 and CD30-positive Reed–Sternberg cells. Most of the patients present with asymptomatic cervical and supraclavicular firm, rubbery and non-tender lymphadenopathy, with or without fever, weight loss, and night sweats [78]. Treatment depends on histology, stage at presentation, number of involved sites, disease bulk, and the presence or absence of constitutional symptoms. Radiation, chemotherapy and surgical excision are available treatment options [79].

e. Childhood Graves' disease

Grave's ophthalmopathy is an autoimmune disorder that may manifest with reasonably significant long-term morbidity [80]. The incidence of this disorder varies from 0.79 to 6.5 per 100000 children in Danish and Hong Kong Chinese populations [81]. Children from age group 0 - 15 years contribute 5 - 6 % of the total patients [82]. Majority of these children have a family history of auto-immune thyroid disease [82], or some other autoimmune endocrine disorder. Children with Down's syndrome have an increased incidence of graves' disease [83]. The patients with this disease have signs ranging from eyelid retraction, chemosis, proptosis, disturbances of ocular motility to sight threatening compressive optic neuropathy which may have long term ophthalmic sequelae both in terms of function and cosmesis. Graves' ophthalmopathy is not very well studied in pediatric patients.

The intensity and severity of ophthalmopathy and myopathy appears to be significantly less intense in children than in adults for unknown reasons, however, lower antibody titres have been suggested as a possible explanation for the same. Ocular manifestations occur commonly in paediatric Graves' disease, but the disease is milder and less intense than in adults. In a study by Chan, Wong, Fan., *et al.* of the 52 patients (62.7%) with positive ocular changes, visual threatening complications or debilitating myopathy was not observed in any patient [84]. Guidelines pertaining to ideal treatment of graves' disease is controversial. The available anti-thyroid drugs include methimazole (MMI), carbimazole (CMZ) and propylthiouracil (PTU) and neither of these drugs, surgery and radioactive iodine (RAI) has been noted to be superior to the other [85]. 1-year remission rates are considerably less in prepubertal (17%) than in pubertal children (30%) when compared based on response to medical management. However, drugs may fail to achieve remission and compliance issues with the drug induced toxicity are other factors of concern. Children are highly susceptible to radiation induced tumorigenesis especially in thyroid gland which is extremely sensitive in this regard. A comprehensive analysis of seven studies pointed to a twofold higher risk of radiation induced carcinoma in the thyroid gland in children under 5 years of age unlike their older counterparts between 5 to 9 years. The risk increased to five times in children between 10 to 14 years [86]. Isolated cases of childhood graves' have also been treated with somatostatin analogs with valuable results and as a substitute to corticosteroid agents and these patients had an improvement in their clinical activity scores. Small risk of thyroid cancer has also been reported with use of radioiodine in children for treating thyrotoxicosis. Surgically, thyroidectomy (subtotal or total) is done in enlarged thyroid gland with large goiter and also in patients with severe thyrotoxicosis [85].

f. Idiopathic inflammatory orbital diseases (Orbital Pseudotumor)

Orbital pseudotumor is an idiopathic condition characterized by a non-granulomatous inflammatory process in the orbit without any local or systemic causes. It commonly manifests with a localized mass within the orbit in 50 % of the cases. This disorder accounts for 11.5 % of cases in paediatric age group out of the total population [87]. The condition is bilateral in 45% of childhood pseudotumor, however, around 90 - 95% cases are unilateral [88]. Patients may present with headache, vomiting, fever, loss of appetite and these symptoms are more common in children [89]. Limitation of ocular motility, swelling of the eyelids, proptosis and increased orbital pressure are amongst the common features of orbital pseudotumor [87]. Total leukocyte count, erythrocyte sedimentation rate, and eosinophilia are noted on blood examination. MRI is superior to CT in view of the radiation risk associated with the latter, and it helps in detecting extra-orbital or intracranial extensions in this disorder. Orbital cellulites, rhabdomyosarcoma, leukemia, orbital trauma, ruptured dermoid cyst, neuroblastoma, metastatic retinoblastoma, lymphangioma and thyroid related orbitopathy are the differential diagnosis to be considered in a child with orbital pseudotumor [88]. Initiation of corticosteroid treatment results in prompt resolution in 75% of the symptoms and signs and is considered of diagnostic significance which can be further confirmed on imaging [90].

g. Pediatric orbital floor fractures

Pediatric orbital floor fractures can present with different profile unlike adult orbital floor fractures and may have serious long-term sequelae if not managed promptly. Injuries caused as a result of high force, yet low velocity target are responsible for pediatric blow out fractures. Children present with severe pain, diplopia, infraorbital anesthesia, with limitation in ocular motility mostly in up-gaze and down-gaze as a result of inferior rectus and inferior oblique involvement. The eye may be enophthalmic with associated sub-conjunctival hemorrhage, ecchymosis and periorbital edema. Bone fracture results in crepitus with hyphaema, epistaxis and the child may have associated traumatic mydriasis or dilatation of the pupil due to third nerve involvement [91]. Diplopia can be annoying and can limit patient functionality considerably and is seen as a result of entrapment or a direct damage of extra-ocular muscles or a neural injury. Periorbital swelling is to a lesser extent in children however the limitation in ocular motility is marked. Immature bones with greater elasticity in children account for trapdoor fractures in children. White-eyed blowout fracture term was named by Jordan and colleagues in 1998 that refers to the patients with post-traumatic orbital floor fractures with limitation in ocular motility to a significant extent without any visible enophthalmos, periorbital soft-tissue edema, and or findings on imaging. CT scan remains the imaging modality of choice however, MRI may be needed in cases where soft tissue entrapment is not apparent on CT scan. Surgery is indicated in cases with symptomatic non-resolving diplopia, muscle or soft tissue entrapment on CT, and positive forced duction test or other clinical evidence of entrapment, oculocardiac reflex (bradycardia, nausea, and syncope), enophthalmos (> 2 mm at presentation), and more than 50 % involvement of the floor of the orbit and no improvement noted on conservative management over several weeks [92]. Early surgical intervention for children with blow out fractures associated with entrapment results in better outcomes than a delayed intervention.

h. Traumatic carotid-cavernous fistula

Carotid-cavernous fistulas (CCF) are classified as traumatic or spontaneous, direct or indirect, and low or high flow. These fistulas are also classified based on their location into 4 types by Barrow: Type A from the ICA, Type B from branches of the ICA, Type C from branches of the external carotid artery (ECA) and Type D combined from branches of the ICA and ECA [93,94].

Patients with CCF present with a classic triad of proptosis, chemosis and orbital bruit. Other clinical manifestations include ophthalmoplegia, visual disturbances, conjunctival injection, intracerebral or a subarachnoid hemorrhage, epistaxis and headache [93,94].

A patient with a fracture of the middle fossa associated with unexplained neurologic findings should undergo a comprehensive work-up to rule out a CCF. Non-invasive imaging with MR or CT angiography can help define the CCF, however, cerebral angiography is considered the gold standard. Management of CCF is based on occlusion of the fistula while maintaining the vascular supply to brain via internal carotid artery and this can be achieved via endovascular techniques such as trans arterial or transvenous embolization using a coil or a liquid embolization and latest modality using a stent. In cases not amenable or with difficult embolization, open surgical approach is performed [95]. 90 % success rates have been achieved.

Other Causes

a. Alternating hemiplegic migraine

Alternating hemiplegic migraine may involve the 3rd or 4th cranial nerves and clinically present with transient migraine like headaches with associated neuropathy along-with diplopia [70]. Alternating hemiplegic migraine is a rare disorder lasting minutes to days with accompanying dystonia, nystagmus, oculomotor abnormalities and cognitive impairment [96].

b. Internuclear ophthalmoplegia (INO)

It is a rare condition in children comprising adduction deficiency in the ipsilateral eye and abducting nystagmus in the contralateral eye. Various causes have been enlisted including benign aqueduct cyst, neoplasms of the brainstem including medulloblastoma, glioma, glioblastoma multiforme, vascular infarcts in the brainstem associated with sickle cell trait, systemic lupus erythematosus, Fabry disease, and periarteritis nodosa. Additional causes of paediatric INO include head trauma, viral meningoencephalitis and brainstem haemorrhage [97]. The diagnosis in children can be difficult because of limited cooperation. Patients need to be followed up closely and treatment of amblyopia is desirable for adequate rehabilitation. Surgical intervention should be sought only in cases not amenable to conservative management.

c. Oculomotor apraxia

It is defined as a disorder of learned movement that is not due to weakness, incoordination, sensory loss or inability to comprehend commands. Presence of this condition indicates a failure to execute a designated action while retaining the ability to carry out the individual components of that action. Atrophy of the parieto-occipital Region and cerebellum is the characteristic feature of Hereditary Ataxia Apraxia Disorders.

d. Vitamin E deficiency

Vitamin E deficiency is known to be associated with various neurologic abnormalities such as ataxia, weakness, areflexia, impaired vision, loss of proprioception, and vibratory sensation and variable ophthalmoplegia [98]. This condition should also be kept in mind in cases posing a diagnostic dilemma for management.

e. Craniosynostosis

Craniosynostosis, a pathological skull malformation that can be denoted as untimely closure of cranial sutures results in an abnormal shaped skull, neurological sequelae and marked orbital facial dysmorphism (Figure 5A-5C) [99]. As the orbit represents a bridge between the face and the cranium, early closure of cranial sutures manifests as craniosynostosis [99]. Craniosynostosis is associated with variety of complications including high intracranial pressure, brain herniation, restrictive brain function, developmental disorders, respiratory diseases, papilledema, strabismus, all of which can cause significant disability in children. Phenotypic classifications of craniosynostosis differentiate between non-syndromic craniosynostosis only involving the skull and syndromic variety which also includes deformity of face and limb anomalies [100]. The prevalence of the condition has been estimated to be about 1 in 2,100 - 2,500 births globally, of which about 80% patients suffer from non-syndromic craniosynostosis, 20% from syndromic craniosynostosis. 10 - 14% cases are genetically transmissible. Most common forms of non-syndromic craniosynostosis are based on the involvement of sagittal, coronal, metopic and lambdoidal suture(s). This isolated craniosynostosis comprises Scaphocephaly (long, narrow skull), Trigenocephaly, Brachycephaly (an abnormally wide head), Synostotic Plagiocephaly and Oxycephaly [101]. More than 180 kinds of syndrome type craniosynostosis have been identified which include Crouzon's syndrome, Apert's syndrome, Pfeiffer's syndrome, Carpenter's syndrome, Muenke's syndrome and Saethre-Chotzen syndrome [102]. Both environmental and genetic factors have been found to play a role in the etio-pathogenesis of these craniofacial malformations [102]. Due to the structural changes in the orbit and increased intracranial pressure, the visual system is more involved in craniosynostosis than any other system. Increased intracranial pressure may occur in the presence of fontanelles and absence of hydrocephalus; pseudo-proptosis can occur due to shallow orbits which may result in corneal exposure, strabismus and ocular motility abnormalities of different types.



Figure 3: 5A: Left lateral view showing increased antero-posterior diameter of the cranium in a child with craniosynostosis; 5B: Right lateral view showing increased antero-posterior diameter in a child with craniosynostosis; 5C: Exotropia in this child with craniosynostosis.

Management

Improved and prompt neuro-surgical treatment has resulted in increased survival. There has been a shift from optic atrophy being previously considered as the main cause of ophthalmic morbidity in affected individuals to amblyopia which occurs as a result of uncorrected refractive errors and strabismus. Incorporation of an ophthalmologist in the multidisciplinary team comprising plastic surgeons, neurosurgeons and maxillofacial surgeons is of paramount importance in preserving vision of the patients [101]. Most important neuro-surgical intervention in craniosynostosis comprises of skull reshaping surgeries, often in stages. Amongst other indications, papilledema, globe luxation and exposure keratopathy were taken as absolute indications to prioritize urgent skull reshaping surgery [101]. Six to twelve months is the preferred age for cranial surgery, which aim to coincide with facial growth and psychosocial development in children. Ophthalmic interventions include correction of refractive errors, amblyopia management and other associated problem like corneal exposure.

Management approach

A step ladder approach helps in managing patients of ophthalmoplegia based on the associated clinical manifestations in a patient. Specific intervention for the particular cause is directed depending on case to case customised basis. If a child of ophthalmoplegia presents with visual loss, one must consider a possibility of an orbital lesion with a compressive neuropathy/a combined orbital with a neurological lesion/Chronic progressive external ophthalmoplegia with retinitis pigmentosa or a traumatic optic neuropathy. If there is no associated visual loss, the aetiology could be neurological including the 3rd, 4th, 6th cranial nerve palsy or a myogenic pathology comprising of myasthenia gravis or muscular dystrophies. Neuroimaging is warranted in all cases of ophthalmoplegia with pupillary involvement. Children with long standing diabetes may manifest with pupillary sparing nerve palsies related to microangiopathy.

Ophthalmoplegia can also be categorised based on the relative extent of ocular motility limitation. If the globe is frozen with no movement, child may have an orbital apex syndrome if the motility limitation is unilateral. In bilateral cases, a possibility of cavernous sinus thrombosis is likely, and a prompt intervention can reduce overall morbidity and mortality. If the limitation of extra-ocular movements is partial, an underlying third nerve palsy in unilateral cases or a thyroid eye disease in bilateral cases is likely.

If the patient has exophthalmos associated with a limitation in ocular motility, an underlying thyroid ophthalmopathy is likely. Sunken or an exophthalmic globe points towards a traumatic orbitopathy/blow-out orbital wall fracture with herniation of the ocular contents. If the ophthalmoplegia has no associated change in ocular position, myasthenia gravis/a myopathy or an underlying congenital cranial dysinnervation syndrome should be considered as likely possibilities.

Ophthalmoplegia with ptosis suggests myasthenia gravis/CPEO/myotonic dystrophy/third nerve palsy/trauma/CFEOM. Concomitant eyelid retraction with ocular motility disturbance is observed with childhood graves or in cases with accompanying proptosis. Orbital inflammatory disease like orbital apex syndrome, cavernous sinus thrombosis, pseudotumor, tumours like lymphomas, naso-pharyngeal carcinoma, pituitary adenoma and panophthalmitis may present with accompanying eyelid edema apart from ophthalmoplegia.

In cases presenting with limitation of extra-ocular movements accompanied by ocular misalignment, a possibility of thyroid eye disease with hypotropia or a complete third nerve palsy should be considered, and appropriate imaging should be ordered to localize the lesion. Bilateral Duane's retraction syndrome or a progressive supranuclear palsy manifest with well aligned eyeballs.

Myasthenia/Thyroid eye disease/or children with complicated strabismus present with painless ophthalmoplegia. Ophthalmoplegia associated with pain needs prompt imaging and intervention since the underlying cause if left untreated may result in significant morbidity and mortality. The causes for painful ophthalmoplegia include third nerve palsy with underlying aneurysms, orbital disease with tumors, carotico-cavernous fistula, cavernous sinus thrombosis or in some cases of ophthalmoplegic migraine.

Management of the patients with specific underlying disorder responsible for ophthalmoplegia requires symptomatic management together with a comprehensive clinical examination, investigations along-with treatment which could be medical or surgical, based on etiology of the condition. Immediate interventions in the form of decompressions or a neuro-surgery may be required in cases where vision is threatened. A period of stable, well recorded deviation (in patients with ophthalmoplegia and ocular misalignment) for a minimum period of 6 months is recommended prior to planning strabismus surgery.

Summary and Conclusions

Pediatric ophthalmoplegia comprises manifestation of a broad domain of neurological and neuro-surgical disorders that are a clinical challenge to the attending neuro-ophthalmologist, strabismologist and paediatric physicians thus necessitating multidisciplinary management approach. This review article highlights the possible etiologist, their presentation and the available management protocols for these ocular motility disorders and to equip the ophthalmologists with the commonalities and differences between childhood and adulthood presentations of ophthalmoplegia and a paediatric perspective of this wide group of ophthalmic condition. In this backdrop, it should also be mentioned that children with conversion disorders and malingering also present with ophthalmoplegia and visual dysfunction conforming to no particular pattern and may pose diagnostic difficulties [73]. A high suspicion of such psychogenic conditions should also be kept in mind. Psychiatric counselling is the modality of management in these cases.

Conflict of Interest

No financial interest or any conflict of interest exists.

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Bibliography

1. Rutstein RP. "Spasm of the near Reflex Mimicking Deteriorating Accommodative Esotropia". *Optometry and Vision Science* 77.7 (2000): 344-346.
2. Cogan DG and CG Freese. "Spasm of the near Reflex". *A.M.A. Archives of Ophthalmology* 54.5 (1955): 752-759.
3. Dagi LR., et al. "Spasm of the near Reflex Associated with Organic Disease". *American Journal of Ophthalmology* 103.4 (1987): 582-585.
4. Galbraith RS. "Incidence of Neonatal Sixth Nerve Palsy in Relation to Mode of Delivery". *American Journal of Obstetrics and Gynaecology* 170.4 (1994): 1158-1159.
5. Goodwin, Denise. "Differential Diagnosis and Management of Acquired Sixth Cranial Nerve Palsy". *Optometry* 77.11 (2006) 534-539.
6. Holmes JM., et al. "Pediatric Third, Fourth, and Sixth Nerve Palsies: A Population-Based Study". *American Journal of Ophthalmology* 127.4 (1999) 388-392.
7. Mekari-Sabbagh ON and RP DaCunha. "Crossed Eyes in a Six-Year-Old Girl". *Survey of Ophthalmology* 45.4 (2001) 331-34.
8. Jafari Alireza K., et al. "Case Report: Duane Retraction Syndrome Associated with Hand Anomaly". *Binocular Vision and Strabismus Quarterly* 25.3 (2010): 159-163.
9. Prats JM., et al. "Congenital Nuclear Syndrome of Oculomotor Nerve". *Pediatric Neurology* 9.6 (1993): 476-478.
10. Noonan CP and M O'Connor. "Surgical Management of Third Nerve Palsy". *The British Journal of Ophthalmology* 79.5 (1995): 431-434.
11. Jampolsky A. "Current Techniques of Adjustable Strabismus Surgery". *American Journal of Ophthalmology* 88.3 (1979): 406-418.
12. Helveston EM., et al. "A New Classification of Superior Oblique Palsy Based on Congenital Variations in the Tendon". *Ophthalmology* 99.10 (1992): 1609-1615.
13. Dhaliwal Avninder., et al. "Third, Fourth, and Sixth Cranial Nerve Palsies Following Closed Head Injury". *Journal of Neuro-Ophthalmology Society* 26.1 (2006): 4-10.

14. Maruo T, *et al.* "Long-Term Results of Surgery for Superior Oblique Palsy". *Japanese Journal of Ophthalmology* 40.2 (1996): 235-238.
15. Bharucha Diana X., *et al.* "MRI Findings in Pediatric Ophthalmoplegic Migraine: A Case Report and Literature Review". *Pediatric Neurology* 37.1 (2007): 59-63.
16. "Headache Classification Committee of the International Headache Society (IHS) The International Classification of Headache Disorders, 3rd Edition". *Cephalalgia: An International Journal of Headache* 38.1 (2018): 1-211.
17. Doran M and AJ Larner. "MRI Findings in Ophthalmoplegic Migraine: Nosological Implications". *Journal of Neurology* 251.1 (2004): 100-01.
18. Gelfand Amy A., *et al.* "Ophthalmoplegic 'migraine' or Recurrent Ophthalmoplegic Cranial Neuropathy: New Cases and a Systematic Review". *Journal of Child Neurology* 27.6 (2012): 759-766.
19. Ogose Takeshi., *et al.* "Ophthalmoplegic Migraine with a Rise in Cytomegalovirus-Specific IgG Antibody". *Pediatrics International* 51.1 (2009): 143-145.
20. Celebisoy N., *et al.* "Ophthalmoplegic Migraine: Two Patients, One at Middle Age with Abducens Palsy". *Cephalalgia: An International Journal of Headache* 25.2 (2005): 151-153.
21. Granado Lig and G Guillen. "Treatment Options for Ophthalmoplegic Migraine". *Journal of Postgraduate Medicine* 55.3 (2009): 231-232.
22. Broomfield Alexander., *et al.* "Paediatric Single Mitochondrial DNA Deletion Disorders: An Overlapping Spectrum of Disease". *Journal of Inherited Metabolic Disease* 38.3 (2015): 445-457.
23. Manea Elena Maria., *et al.* "Pearson Syndrome in the Neonatal Period: Two Case Reports and Review of the Literature". *Journal of Pediatric Hematology/Oncology* 31.12 (2009): 947-951.
24. Yu Meng., *et al.* "Diagnosis and Management of Kearns-Sayre Syndrome Rely on Comprehensive Clinical Evaluation". *Chinese Medical Journal* 129.20 (2016): 2519-2520.
25. Liu I Ting., *et al.* "Preseptal and Orbital Cellulitis: A 10-Year Review of Hospitalized Patients". *Journal of the Chinese Medical Association: JCMS* 69.9 (2006): 415-422.
26. Askanas V and WK Engel. "Sporadic Inclusion-Body Myositis and Hereditary Inclusion-Body Myopathies: Diseases of Oxidative Stress and Aging?". *Archives of Neurology* 55.7 (1998): 915-920.
27. Watts Giles DJ., *et al.* "Inclusion Body Myopathy Associated with Paget Disease of Bone and Frontotemporal Dementia Is Caused by Mutant Valosin-Containing Protein". *Nature Genetics* 36.4 (2004): 377-381.
28. Calado A., *et al.* "Nuclear Inclusions in Oculopharyngeal Muscular Dystrophy Consist of poly(A) Binding Protein 2 Aggregates Which Sequester poly(A) RNA". *Human Molecular Genetics* 9.15 (2000): 2321-2328.
29. Minami N., *et al.* "Oculopharyngodistal Myopathy Is Genetically Heterogeneous and Most Cases Are Distinct from Oculopharyngeal Muscular Dystrophy". *Neuromuscular Disorders: NMD* 11.8 (2001): 699-702.

30. Brais B., *et al.* "Short GCG Expansions in the PABP2 Gene Cause Oculopharyngeal Muscular Dystrophy". *Nature Genetics* 18.2 (1998): 164-167.
31. Moraes CT., *et al.* "mtDNA Depletion with Variable Tissue Expression: A Novel Genetic Abnormality in Mitochondrial Diseases". *American Journal of Human Genetics* 48.3 (1991): 492-501.
32. Schaefer Andrew M., *et al.* "The Epidemiology of Mitochondrial Disorders--Past, Present and Future". *Biochimica Et Biophysica Acta* 1659.2-3 (2004): 115-20.
33. Mancuso Michelangelo., *et al.* "Mitochondrial Myopathy of Childhood Associated with Mitochondrial DNA Depletion and a Homozygous Mutation (T77M) in the TK2 Gene". *Archives of Neurology* 60.7 (2003): 1007-1009.
34. El-Hattab Ayman W and Fernando Scaglia. "Mitochondrial DNA Depletion Syndromes: Review and Updates of Genetic Basis, Manifestations, and Therapeutic Options". *Neurotherapeutics: The Journal of the American Society for Experimental NeuroTherapeutics* 10.2 (2013): 186-198.
35. Oskoui Maryam., *et al.* "Clinical Spectrum of Mitochondrial DNA Depletion due to Mutations in the Thymidine Kinase 2 Gene". *Archives of Neurology* 63.8 (2006): 1122-1126.
36. Saada Ann., *et al.* "mtDNA Depletion Myopathy: Elucidation of the Tissue Specificity in the Mitochondrial Thymidine Kinase (TK2) Deficiency". *Molecular Genetics and Metabolism* 79.1 (2003): 1-5.
37. Bourdon Alice., *et al.* "Mutation of RRM2B, Encoding p53-Controlled Ribonucleotide Reductase (p53R2), Causes Severe Mitochondrial DNA Depletion". *Nature Genetics* 39.6 (2007): 776-780.
38. Traboulsi Elias I. "Congenital Abnormalities of Cranial Nerve Development: Overview, Molecular Mechanisms, and Further Evidence of Heterogeneity and Complexity of Syndromes with Congenital Limitation of Eye Movements". *Transactions of the American Ophthalmological Society* 102 (2004): 373-389.
39. Bosley Thomas M., *et al.* "The Clinical Spectrum of Homozygous HOXA1 Mutations". *American Journal of Medical Genetics Part A* 146A.10 (2008): 1235-1240.
40. Engle Elizabeth C. "The Genetic Basis of Complex Strabismus". *Pediatric Research* 59.3 (2006): 343-348.
41. Engle EC., *et al.* "Oculomotor Nerve and Muscle Abnormalities in Congenital Fibrosis of the Extraocular Muscles". *Annals of Neurology* 41.3 (1997): 314-325.
42. Engle EC., *et al.* "Mapping a Gene for Congenital Fibrosis of the Extraocular Muscles to the Centromeric Region of Chromosome 12". *Nature Genetics* 7.1 (1994): 69-73.
43. Yamada Koki., *et al.* "Heterozygous Mutations of the Kinesin KIF21A in Congenital Fibrosis of the Extraocular Muscles Type 1 (CFEOM1)". *Nature Genetics* 35.4 (2003): 318-321.
44. Nakano M., *et al.* "Homozygous Mutations in ARIX(PHOX2A) Result in Congenital Fibrosis of the Extraocular Muscles Type 2". *Nature Genetics* 29.3 (2001): 315-320.
45. Bosley Thomas M., *et al.* "Neurological Features of Congenital Fibrosis of the Extraocular Muscles Type 2 with Mutations in PHOX2A". *Brain: A Journal of Neurology* 129.9 (2006): 2363-2374.

46. Tischfield Max A., *et al.* "Human TUBB3 Mutations Perturb Microtubule Dynamics, Kinesin Interactions, and Axon Guidance". *Cell* 140.1 (2010): 74-87.
47. Oystreck Darren T., *et al.* "Recent Progress in Understanding Congenital Cranial Dysinnervation Disorders". *Journal of Neuro-Ophthalmology* 31.1 (2011): 69-77.
48. Fels Rebecca. "Congenital Cranial Dysinnervation Disorders: A Literature Review". *The American Orthoptic Journal* 67.1 (2017): 89-92.
49. Evoli A., *et al.* "Juvenile Myasthenia Gravis with Prepubertal Onset". *Neuromuscular Disorders: NMD* 8.8 (1998): 561-567.
50. Lee Ju-Yeun., *et al.* "Transient Neonatal Myasthenia Gravis due to a Mother with Ocular Onset of Anti-Muscle Specific Kinase Myasthenia Gravis". *Neuromuscular Disorders: NMD* 27.7 (2017): 655-657.
51. Beeson D., *et al.* "Congenital Myasthenic Syndromes". *Current Opinion in Neurology* 10.5 (1997): 402-07.
52. Kostera-Pruszczyk Anna and Hubert Kwiecinski. "Juvenile Seropositive Myasthenia Gravis with Anti-MuSK Antibody after Thymectomy". *Journal of Neurology* 256.10 (2009): 1780-1781.
53. Pitt Matthew. "Neurophysiological Strategies for the Diagnosis of Disorders of the Neuromuscular Junction in Children". *Developmental Medicine and Child Neurology* 50.5 (2008): 328-333.
54. Gronseth GS and RJ Barohn. "Practice Parameter: Thymectomy for Autoimmune Myasthenia Gravis (an Evidence-Based Review): Report of the Quality Standards Subcommittee of the American Academy of Neurology". *Neurology* 55.1 (2000): 7-15.
55. Sanders DB., *et al.* "Clinical Aspects of MuSK Antibody Positive Seronegative MG". *Neurology* 60.12 (2003): 1978-1980.
56. Schneider-Gold C., *et al.* "Corticosteroids for Myasthenia Gravis". *The Cochrane Database of Systematic Reviews* 2 (2005): CD002828.
57. Monsul Nicholas T., *et al.* "The Effect of Prednisone on the Progression from Ocular to Generalized Myasthenia Gravis". *Journal of the Neurological Sciences* 217.2 (2004): 131-133.
58. Sommer N., *et al.* "Ocular Myasthenia Gravis: Response to Long-Term Immunosuppressive Treatment". *Journal of Neurology, Neurosurgery, and Psychiatry* 62.2 (1997): 156-162.
59. Hart IK., *et al.* "Immunosuppressive Agents for Myasthenia Gravis". *The Cochrane Database of Systematic Reviews* 4 (2007): CD005224.
60. Hehir Michael K., *et al.* "Mycophenolate Mofetil in AChR-Antibody-Positive Myasthenia Gravis: Outcomes in 102 Patients". *Muscle and Nerve* 41.5 (2010): 593-598.
61. Wylam Mark E., *et al.* "Successful Treatment of Refractory Myasthenia Gravis Using Rituximab: A Pediatric Case Report". *The Journal of Pediatrics* 143.5 (2003): 674-77.
62. Gajdos P., *et al.* "Clinical Trial of Plasma Exchange and High-Dose Intravenous Immunoglobulin in Myasthenia Gravis. Myasthenia Gravis Clinical Study Group". *Annals of Neurology* 41.6 (1997): 789-796.
63. Kapur R., *et al.* "MR Imaging of Orbital Inflammatory Syndrome, Orbital Cellulitis, and Orbital Lymphoid Lesions: The Role of Diffusion-Weighted Imaging". *AJNR. American Journal of Neuroradiology* 30.1 (2009): 64-70.
64. Pandian Datta G., *et al.* "Nine Years' Review on Preseptal and Orbital Cellulitis and Emergence of Community-Acquired Methicillin-Resistant Staphylococcus Aureus in a Tertiary Hospital in India". *Indian Journal of Ophthalmology* 59.6 (2011): 431-35.

65. Rudloe Tiffany F, *et al.* "Acute Periorbital Infections: Who Needs Emergent Imaging?" *Pediatrics* 125.4 (2010): e719-726.
66. Lee Seongmu and Michael T Yen. "Management of Preseptal and Orbital Cellulitis". *Saudi Journal of Ophthalmology* 25.1 (2011): 21-29.
67. Zanus C., *et al.* "The Tolosa-Hunt Syndrome in Children: A Case Report". *Cephalalgia: An International Journal of Headache* 29.11 (2009): 1232-1237.
68. Kline L B and JG Galbraith. "Parasellar Epidermoid Tumor Presenting as Painful Ophthalmoplegia". *Journal of Neurosurgery* 54.1 (1981): 113-117.
69. O' Connor Ged and Michael Hutchinson. "Tolosa-Hunt Syndrome Responsive to Infliximab Therapy". *Journal of Neurology* 256.4 (2009): 660-661.
70. Sharma Tarun., *et al.* "Intraocular Cysticercosis: Clinical Characteristics and Visual Outcome after Vitreoretinal Surgery". *Ophthalmology* 110.5 (2003): 996-1004.
71. Pushker Neelam., *et al.* "Orbital and Adnexal Cysticercosis". *Clinical and Experimental Ophthalmology* 30.5 (2002): 322-33.
72. Ayan I and M Altun. "Nasopharyngeal Carcinoma in Children: Retrospective Review of 50 Patients". *International Journal of Radiation Oncology, Biology, Physics* 35.3 (1996): 485-492.
73. Orbach, Daniel, *et al.* "Radiation and Chemotherapy Combination for Nasopharyngeal Carcinoma in Children: Radiotherapy Dose Adaptation after Chemotherapy Response to Minimize Late Effects". *Pediatric Blood and Cancer* 50.4 (2008): 849-853.
74. Humpl T., *et al.* "Rhabdomyosarcoma of the orbits in childhood". *Der Ophthalmologe: Zeitschrift Der Deutschen Ophthalmologischen Gesellschaft* 94.12 (1997): 914-919.
75. Toro Jorge R., *et al.* "Incidence Patterns of Soft Tissue Sarcomas, regardless of Primary Site, in the Surveillance, Epidemiology and End Results Program, 1978-2001: An Analysis of 26,758 Cases". *International Journal of Cancer* 119.12 (2006): 2922-2930.
76. Sjö Lene Dissing. "Ophthalmic Lymphoma: Epidemiology and Pathogenesis". *Acta Ophthalmologica* 87.1 (2009): 1-20
77. Sandlund JT, *et al.* "Non-Hodgkin's Lymphoma in Childhood". *The New England Journal of Medicine* 334.19 (1996): 1238-48.
78. Smith Ron S., *et al.* "Prognostic Factors for Children with Hodgkin's Disease Treated with Combined-Modality Therapy". *Journal of Clinical Oncology* 21.10 (2003): 2026-2033.
79. Olson Michael R and Sarah S Donaldson. "Treatment of Pediatric Hodgkin Lymphoma". *Current Treatment Options in Oncology* 9.1 (2008): 81-94.
80. Carter JA and RD Utiger. "The Ophthalmopathy of Graves' Disease". *Annual Review of Medicine* 43 (1992): 487-495.
81. Perrild H., *et al.* "Clinical Aspects and Treatment of Juvenile Graves' Disease". *Experimental and Clinical Endocrinology and Diabetes* 105.4 (1997): 55-57.
82. Saxena KM., *et al.* "childhood thyrotoxicosis: a long-term perspective". *British Medical Journal* 2.5418 (1964): 1153-1158.
83. Friedman JM and P J Fialkow. "The Genetics of Graves' Disease". *Clinics in Endocrinology and Metabolism* 7.1 (1978): 47-65.

84. Chan W, et al. "Ophthalmopathy in Childhood Graves' Disease". *The British Journal of Ophthalmology* 86.7 (2002): 740-742.
85. Krassas GE. "Treatment of Juvenile Graves' Disease and Its Ophthalmic Complication: The European Way". *European Journal of Endocrinology* 150.4 (2004): 407-414.
86. Ron Elaine, et al. "Thyroid Cancer after Exposure to External Radiation: A Pooled Analysis of Seven Studies. 1995". *Radiation Research* 178.2 (2012): AV43-AV60.
87. Yan Jianhua, et al. "Idiopathic Orbital Inflammatory Pseudotumor in Chinese Children". *Orbit (Amsterdam, Netherlands)* 25.1 (2006): 1-4.
88. Berger JW, et al. "Pediatric Orbital Pseudotumor: Case Report and Review of the Literature". *International Ophthalmology Clinics* 36.1 (1996): 161-177.
89. Stevens JL, et al. "Pseudotumor of the Orbit in Early Childhood". *Journal of American Association for Pediatric Ophthalmology and Strabismus* 2.2 (1998): 120-123.
90. Hankey GJ, et al. "Orbital Myositis: A Study of Six Cases". *Australian and New Zealand Journal of Medicine* 17.6 (1987): 585-591.
91. Kim Jungwan, et al. "Endoscope-Assisted Repair of Pediatric Trapdoor Fractures of the Orbital Floor: Characterization and Management". *The Journal of Craniofacial Surgery* 21.1 (2010): 101-05.
92. Burnstine Michael A. "Clinical Recommendations for Repair of Isolated Orbital Floor Fractures: An Evidence-Based Analysis". *Ophthalmology* 109.7 (2002): 1207-1210.
93. Fattahi Tirbod T, et al. "Traumatic Carotid-Cavernous Fistula: Pathophysiology and Treatment". *The Journal of Craniofacial Surgery* 14.2 (2003): 240-246.
94. Ellis Jason A, et al. "Carotid-Cavernous Fistulas". *Neurosurgical Focus* 32.5 (2012): E9.
95. Gemmete Joseph J, et al. "Endovascular Techniques for Treatment of Carotid-Cavernous Fistula". *Journal of Neuro-Ophthalmology* 29.1 (2009): 62-71.
96. Levin Morris and Thomas N Ward. "Ophthalmoplegic Migraine". *Current Pain and Headache Reports* 8.4 (2004): 306-309.
97. Rizzo Jennifer L, et al. "Pediatric Internuclear Ophthalmoplegia". *Journal of Neuro-Ophthalmology* 33.2 (2013): 134-136.
98. Rosenblum, J. L., et al. "A Progressive Neurologic Syndrome in Children with Chronic Liver Disease". *The New England Journal of Medicine* 304.9 (1981): 503-508.
99. Anantheswar Y N and NK Venkataramana. "Pediatric Craniofacial Surgery for Craniosynostosis: Our Experience and Current Concepts: Part -1". *Journal of Pediatric Neurosciences* 4.2 (2009): 86-99.
100. Wang AK and XLKang. "[Craniosynostosis and strabismus]". *[Zhonghua Yan Ke Za Zhi] Chinese Journal of Ophthalmology* 52.8 (2016): 626-630.

101. Pattisapu Jogi V, *et al.* "Craniosynostosis: Diagnosis and Surgical Management". *Atlas of the Oral and Maxillofacial Surgery Clinics of North America* 18.2 (2010): 77-91.
102. Ciurea Alexandru Vlad and Corneliu Toader. "Genetics of Craniosynostosis: Review of the Literature". *Journal of Medicine and Life* 2.1 (2009): 5-17.

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